

Implementing a CYP2C19-guided approach for prescribing dual antiplatelet therapy in acute coronary syndrome for patients undergoing percutaneous coronary intervention: a cost-effectiveness analysis

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Abstract

Background

Prescribing guidelines recommend prasugrel or ticagrelor with aspirin as dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS), with clopidogrel reserved for people at high bleeding risk or with contraindications. We evaluated the cost-effectiveness of a point-of-care *CYP2C19* genetic test to guide prescribing of DAPT compared with current prescribing practice in the NHS in England (NHS).

Methods

We designed a hybrid decision-tree and state transition Markov model (40-year horizon) to calculate the costs and Quality-Adjusted Life-Years (QALYs) of CYP2C19-guided DAPT compared with current prescribing for two post-PCI populations: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction or unstable angina (UA/NSTEMI). In CYP2C19-guided DAPT, LoF carriers were prescribed prasugrel or ticagrelor; non-LoF carriers prescribed clopidogrel. Costs (£, 2024/25 prices, NHS and Social Services), event rates, and utility values were sourced from published data. Sensitivity analyses measured uncertainty in the analysis results. The model was built in R (available on GitHub).

Results

CYP2C19-guided DAPT generated an additional 0.0439 QALYs at an additional cost of £25 for STEMI, giving an incremental cost-effectiveness ratio (ICER) of £569 per QALY. In UA/NSTEMI, CYP2C19-guided DAPT generated an additional 0.0358 QALYs at an additional cost of £83, giving an ICER of £2,318 per QALY. At a cost-effectiveness threshold of £20,000 per QALY, CYP2C19-guided DAPT had a probability of being cost-effective of 87.6% in the STEMI population and 94.3% in the UA/NSTEMI population.

Conclusions

CYP2C19-guided DAPT was a cost-effective use of the NHS budget when compared with current prescribing practice for both STEMI and UA/NSTEMI populations.

Background

Current European guidelines[1] together with prescribing guidelines in England[2] define the appropriate management of acute coronary syndromes in people undergoing percutaneous coronary intervention (hereafter ACS-PCI). In England, the national guideline for managing acute coronary syndrome (NG185)[2] recommends using a P2Y₁₂-inhibitor (either prasugrel or ticagrelor) with aspirin as first-line dual antiplatelet therapy (DAPT) for people with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). In people for whom bleeding risk is a concern, such as following a previous stroke or intracranial haemorrhage, being older (75 years or over) or taking medicines for anti-coagulation, offering clopidogrel with aspirin is the preferred approach[2].

Since 2010, there has been a temporal shift in prescribing patterns for ACS-PCI with a marked increase in the use of the newer P2Y₁₂-inhibitors, especially ticagrelor. The use of prasugrel has accelerated more recently since 2020 following the publication of a seminal trial[3]. The P2Y₁₂-inhibitors (ticagrelor; prasugrel) are more expensive (49-fold and 28-fold, respectively) than the clopidogrel[4] with an increased risk of side-effects, most notably bleeding, dyspnoea and heart problems (ventricular pauses)[5]. These side-effects are usually self-limiting, but they contribute to a higher discontinuation rate for ticagrelor when compared with clopidogrel[6]. Some randomised controlled trials have demonstrated the superiority of P2Y₁₂ inhibitors in selected populations but data representing prescribing in practice have not consistently confirmed a safety or effectiveness advantage over clopidogrel[7].

There is emerging trial-based [8]and practice-based[9] evidence that testing for variants of the *CYP2C19* gene that encodes the CYP450-2C19 (CYP2C19) enzyme which metabolises the pro-drug, clopidogrel, into its active form offers a strategy for choosing the relevant medicine to use in a DAPT regimen for ACS-PCI. Testing for the variant of the *CYP2C19* gene can be done in a laboratory or at the point-of-care. When prescribing a DAPT time is of the essence to starting therapy and so using a point-of-care test is crucial[10]. Using point-of-care CYP2C19 testing in the prescribing pathway for ACS-PCI enables a strategy to guide selection of individuals who can safely and effectively be offered clopidogrel instead of a P2Y₁₂-inhibitor [ref: Popular trial]. Using CYP2C19-guided prescribing of DAPT (hereafter 'CYP2C19-guided

DAPT) in this way to decide whether clopidogrel is an option is termed 'genotype guided de-escalation' which has the potential to reduce the chance of bleeding without increasing ischaemic risk when compared with using a P2Y₁₂-inhibitor in the DAPT regimen[11, 12].

In the NHS in England, implementing CYP2C19-guided DAPT offers a potential approach to select the most safe and effective medicine for ACS-PCI. There is evidence to suggest that de-escalation to using clopidogrel rather than a P2Y₁₂-inhibitor can potentially reduce bleeding complications and lower readmissions to hospital and save public money[5, 13]. For example, studies evaluating the cost-effectiveness of CYP2C19-guided DAPT in The Netherlands[14, 15], US[16–18], have suggested that this strategy is a good use of health care resources in these settings. There are no published studies that have identified the cost-effectiveness of CYP2C19-guided DAPT for ACS-PCI in the health care system in England. The aim of this study is to identify the health care costs and health consequences of implementing CYP2C19 testing at the point-of-prescribing DAPT (CYP2C19-guided DAPT) for ACS-PCI in two relevant population (STEMI; UA/NSTEMI) compared with current prescribing practice in England.

Methods

We designed a decision-analytic cost-effectiveness model to address the pre-defined decision problem using the specified design criteria (Table 1). The model structure was conceptualised in accordance with the best practice recommendations for the development and validation of model-based economic evaluations[19, 20]. The study is reported in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) guidelines (see Supplementary Appendix 1) [21]. Ethical approval was not required as all data were obtained from existing sources.

Table 1
Key decision and design criteria

Criteria	Description
Decision problem	To evaluate whether CYP2C19 testing to guide dual antiplatelet therapy (DAPT) is cost-effective when compared with standard care for patients with acute coronary syndrome (ACS) undergoing PCI within the National Health Service in England. Separate analyses were conducted for patients with STEMI and UA/NSTEMI.
Population	Patients with acute coronary syndrome (ACS) undergoing PCI were modelled separately for STEMI and UA/NSTEMI. • STEMI: males, mean age 62 years (75%); females, mean age 69 years (25%). • UA/NSTEMI: males, mean age 64 years (72%); females, mean age 69 years (28%).
Intervention	CYP2C19 genetic testing to guide antiplatelet therapy. Treatment allocation was stratified by metaboliser status: - Non-Loss-of-Function carriers (normal, rapid, or ultra-rapid metabolisers): clopidogrel 75 mg once daily plus aspirin 75 to 150 mg once daily (clopidogrel loading dose 300 to 600 mg), continued for 12 months. - Loss-of-Function carriers (intermediate or poor metabolisers): ticagrelor 90 mg twice daily plus aspirin 75 to 150 mg once daily (ticagrelor loading dose 180 mg), or prasugrel 5 to 10 mg once daily plus aspirin 75 to 150 mg once daily (prasugrel loading dose 60 mg), continued for 12 months
Comparator	Current prescribing, defined as dual antiplatelet therapy (DAPT) with aspirin plus one of the following P2Y₁₂ inhibitors for 12 months: - Ticagrelor: 90 mg twice daily plus aspirin 75 to 150 mg once daily (loading dose: ticagrelor 180 mg). - Prasugrel: 5 to 10 mg once daily plus aspirin 75 to 150 mg once daily (loading dose: prasugrel 60 mg). - Clopidogrel: 75 mg once daily plus aspirin 75 to 150 mg once daily (loading dose: clopidogrel 300 to 600 mg).
Health consequences	Major and minor bleeding, reinfarction, non-fatal stroke, dyspnoea, death, and QALYs
Decision model	Two-part model: short-term (on-year) decision tree and long-term (lifetime) state-transition Markov model
Study perspective	National Health Service in England
Time horizon	Life-time horizon
Cycle length	1-year
Price year (currency)	2024/2025 (£)
Discounting	Discount rate of 3.5% per annum for both costs and health consequences
Software	The model was developed and implemented in R.
Resource use	All costs were assessed from the perspective of the NHS and Social Services. Unit costs were obtained from National Health Service tariffs and PSSRU Adjusted to 2024/25 prices using the appropriate inflation indices.
Analysis outputs	Expected costs, life years, and QALYs, as well as incremental net monetary benefit (NMB).
Uncertainty	Uncertainty was explored using deterministic one-way, scenario and probabilistic sensitivity analysis (PSA).
Cost-effectiveness threshold	£20,000 per QALY gained (NICE recommended threshold ¹)
¹ NICE health technology evaluations: the manual (PMG36), last updated 23 Oct 2025. Abbreviations: STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; NICE = National Institute for Health and Care Excellence; UA = unstable angina; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year.	

<< Table 1 here

Population

The relevant population for this analysis was people with ACS needing PCI comprising those who have experienced STEMI or UA/NSTEMI. All people with ACS were assumed to be candidates for PCI and eligible for 12-months of DAPT. Because baseline risks of clinical events differ between people with STEMI and those with NSTEMI or unstable angina, we modelled these as two separate populations (see Table 1) in two distinct analyses, but using the same decision-analytic model structure[2].

Intervention

The intervention of interest was defined as a test to identify the genotype of *CYP2C19* encoding the CYP2C19 enzyme (CYP2C19-guided DAPT) to inform the relevant strategy for treating ACS-PCI in two populations (STEMI; UA/NSTEMI). In the CYP2C19-guided DAPT strategy, each person was assumed to be offered a test at the point of prescribing in hospital (point-of-care testing) when the PCI was performed. This analysis assumed that CYP2C19 point-of-care genotyping was provided using the GeneDrive test (GeneDrive PLC, Manchester, UK). The GeneDrive *CYP2C19* test is a portable, point-of-care testing platform developed and validated[22] to detect key *CYP2C19* loss- and gain-of-function alleles directly from a buccal swab sample. The system requires minimal operator training, with the testing process completed in approximately 80 minutes. Test results were assumed to be available within 80-minutes.

If an individual in the CYP2C19-guided DAPT strategy was identified to be carrying a loss-of-function *CYP2C19* allele (LoF) they were prescribed aspirin and then either ticagrelor or prasugrel. In the analysis, the use of ticagrelor or prasugrel was represented by a proportion of the total population being offered one of the P2Y₁₂-inhibitors. Non-carriers of LoF were assumed to be prescribed aspirin and clopidogrel.

Comparator

The comparator strategy for this analysis was defined to represent standard prescribing for ACS-PCI. The choice between ticagrelor, prasugrel or clopidogrel and aspirin was assumed to be made by the treating cardiologist in the hospital according to published clinical guidelines[2] supported by individual patient factors. The analysis assumed prescribing patterns using data from the British Cardiovascular Intervention Society (BCIS) national audit from study by Mohamed et al[1].

Decision-analytic model

A decision-analytic model structure was co-designed and applied separately for the study STEMI and UA/NSTEMI populations, using population-specific risk inputs to address the decision-problem and meet the design criteria in Table 1. Model conceptualisation followed published guidance for good modelling practice[23]. A rapid review of relevant economic evaluations identified 16 studies [ref], which were used to inform the model structure and parameters. The co-design process involved four analysts working with six clinical experts; representing pharmacogenetics (n = 2), clinicians who prescribe DAPT (n = 4). The analysts first described the relevant pathways for the intervention and comparator component of the decision-analytic model. They then met with the clinical experts and people with knowledge of ACS separately on four occasions. The final decision-analytic model structure used a decision tree combined with a state transition Markov (hereafter 'Markov') model (see Fig. 1)

<<Figure 1 here

Decision-tree

The decision-tree represented the first 12 months following the decision to start a medicine for ACS-PCI. One decision branch represented current prescribing practice, while the other decision branch represented the decision to start an individual on a medicine informed by CYP2C19-guided DAPT. In the branch representing CYP2C19-guided DAPT, the analysis allowed for scenarios in which the test was not ordered or results acted upon; in which case treatment defaulted to the current prescribing practice. The decisions to order and act on test results were taken in sequence and independently for each individual. The decision-tree accounted for six possible short-term (12-months) outcomes: myocardial infarction; stroke; minor and major bleeding; dyspnoea; death (Fig. 1A).

Markov model

On moving through the first 12-months of each pathway, individuals then entered the Markov model that represented the health events (states) that might occur over their remaining lifetime (40-year horizon; annual cycle length). The Markov model represented six (health) states: no further health event; reinfarction; post-reinfarction; stroke; post-stroke; death (from a cardiac event; or any cause). All individuals entered the Markov model in the health states corresponding to their status at the end of the decision tree. Events were assumed to occur mid-cycle; therefore, a mid-cycle correction was applied by averaging the values (costs; utilities) for no-event and event. Individuals were assumed to experience only one event in the first year post-PCI[2]. Movement between health states in the Markov model was captured using 'state-transition' probabilities, derived from risks observed between 31-days and one-year and applied uniformly across subsequent cycles (at one-year intervals) through the model (see Supplementary Appendix 2). Mortality was modelled separately using age- and sex-

specific life tables for England [24], adjusted with health-state-specific standardised mortality ratios (SMRs) obtained from published evidence[25].

Clinical inputs

We populated the decision-analytic model with clinical inputs for the two distinct analyses (STEMI; UA/NSTEMI) covering: cohort characteristics (distinct STEMI and UA/NSTEMI cohorts); prescribing patterns; point-of-care test uptake; baseline event risks (mortality, reinfarction, stroke, bleeding, dyspnoea); treatment effects; long-term progression (post-year-1 transitions and mortality adjustments). Full parameter numerical values, and distributional assumptions are reported in the Supplementary Appendix 2).

Prescribing patterns

Current prescribing practice was informed by the British Cardiovascular Intervention Society (BCIS) Audit report to reflect NHS practice[1]. Risk of reinfarction, stroke, death, bleeding and dyspnoea under aspirin with clopidogrel were anchored to UK registry and observational study data for the first year after the index event and specified separately for STEMI and UA/NSTEMI[26–28].

Treatment effectiveness and side-effects

Point-of-care test uptake

In the CYP2C19-guided DAPT strategy, the probability of ordering and following the genetic test was obtained from a UK preference-based study[29] of clinicians' views. The prevalence of CYP2C19 LoF alleles was taken from a large US cohort[30], cross validated with two local cohorts in relevant populations[31, 32] and weighted by UK ethnic distribution taken from Office for National Statistics report (2022)[24] to reflect population variability.

Baseline event risks

Risks of ischaemic events, bleeding, and dyspnoea associated with ticagrelor and prasugrel were assumed to be equal irrespective of treatment strategy. For individuals without an LoF allele who received clopidogrel, relative risks of ischaemic events and bleeding were taken from a meta-analysis by Pereira et al[11].

Treatment effects

The analysis assumed the same relative treatment effects for STEMI and UA/NSTEMI populations[2]. The treatment effectiveness for ticagrelor and prasugrel was taken from a network meta-analysis published in NICE NG185 evidence review[2]. Adverse events comprised bleeding and dyspnoea and were included for all treatment arms, with increased risk in the ticagrelor arm parameterised using odds ratios from a network meta-analysis[2]. These adverse events were treated as first year (acute) consequences only and were not carried forward into the long-term Markov phase, as they were not considered prognostic for survival, health-related quality of life, or costs beyond first year[33]. The analysis assumed that treatment effects did not extend beyond the one-year follow-up, as all individuals were considered to continue aspirin monotherapy. This simplified assumption reflected the limited availability of robust data on multiple downstream events and is consistent with approaches adopted in published decision-analytic models for cardiovascular disease, in England[2, 34].

Health consequences

The health consequences for CYP2C19-guided DAPT and current prescribing were captured using life-years and quality-adjusted life-years. Life-years were calculated by summing the time spent in all alive health states across Markov model cycles. To calculate QALYs, each health state in the Markov model was assigned a utility value to represent the health-related quality of life (quality-adjustment) of being in that 'event'. The following health state utility values were needed for this analysis: no-cardiac event; reinfarction; post-reinfarction; stroke; post-stroke (Supplementary Appendix2 TableS2.1). Utilities were adjusted for the age and sex distribution of STEMI and UA/NSTEMI patients using the formula published by Ara and colleagues[35]. Utility decrements for major and minor bleeding, and their assumed duration within 12-months, were taken from NICE NG185 based on Doble [36]. For those who experiencing dyspnoea, a decrement was applied for four weeks in the first year, using the disutility value from Kazi et al[18] and duration from the DISPERSE-2 trial[37]. Utilities were applied to each health state and multiplied by the time spent in that state; these products were then summed across states over the model horizon to yield quality-adjusted life-years (QALYs).

Resource use and costs

The relevant items of resource use for the chosen study perspective (NHS and Social Services) were identified for each branch of the decision tree and state in the Markov model. Health care costs were calculated by multiplying each item of resource use by a unit cost.

Supplementary Appendix 2 shows each item of resource use and the source for each unit cost. Each medicine was assumed to be taken for a total treatment period as: 328 days for everyone who survived one year without an ischaemic event [Schulz]; 365 days for those who experienced an ischaemic event; 182 days for individuals who died within the first year (i.e. individuals are assumed to die halfway through the year on average). Costs were inflated using health service-specific indices from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2024/25 edition). Unit costs for the CYP2C19 point-of-care test were provided by the manufacturer of the test (GeneDrive) and included the analyser, consumables, and supporting materials.

Main analysis

The main analysis calculated the total expected health care costs, life-years and QALYs for the CYP2C19-guided DAPT strategy and for current prescribing practice, applying a discount rate of 3.5% to both costs and QALYs. An incremental analysis then compared the difference in total costs, life-years and QALYs. If the incremental costs and QALYs were both found to be positive, then an incremental cost per QALY gained was calculated using the formula:

$$ICER = \frac{(Cost_{CYP2C19-guidedDAPT} - Cost_{current})}{(QALY_{CYP2C19-guidedDAPT} - QALY_{current})}$$

Where: QALY is the cumulative Quality Adjusted Life Years, and costs are the total Health care costs generated by the two competing strategies over long term which both discounted at an annual rate of 3.5%. The resulted incremental cost-effectiveness ratio (ICER) was compared to the current threshold of acceptability used in the context of the NHS (£20,000 per QALY gained).

Incremental net monetary benefit (NMB) was calculated per patient and for the total population[38]. Where NMB represents the monetary value of health gains from the intervention, offset by its incremental costs, and can be calculated using this formula:

$$NMB = (\Delta QALY \times \lambda) - \Delta Cost$$

where λ is the NICE cost-effectiveness threshold (£20,000 per QALY) and $\Delta QALY$ is the incremental QALYs gained with CYP2C19-guided strategy and $\Delta Cost$ is the incremental cost of CYP2C19-guided DAPT strategy when compared with current practice. Firstly, we calculated per/person NMB and then scaled these results up to the population level by multiplying the per-person NMB by the number of STEMI and UA/NSTEMI populations in England expected to receive testing. A positive NMB means the testing strategy delivers more health for the NHS than it costs[38].

Sensitivity and scenario analyses

Deterministic one-way sensitivity analyses assessed the impact of varying 28 parameters to prespecified values, with results summarised in a tornado diagram (Supplementary Appendix 4). We also examined 13 different scenarios reflecting treatment practice (alternative distributions of antiplatelet prescribing), cost inputs (drug prices, point-of-care testing, and management of minor and major bleeding) implementation (e.g. test ordering and clinician use of results), and methodological choices (discount rates for costs and health outcomes). A scenario analysis also looked at the impact of not applying a discount rate to the costs and QALYs.

Probabilistic sensitivity analysis (PSA) using 100,000 simulations was undertaken to assess the joint impact of uncertainty in clinical, cost, and utility inputs across 41 model parameters (Supplementary Appendix 2). In each iteration, uncertain parameters were sampled simultaneously from their assigned probability distributions to reflect parameter uncertainty, and the model was run to estimate total costs and QALYs for each strategy. Incremental costs, incremental QALYs, and the corresponding ICER were then calculated for that iteration, generating empirical distributions of the main outcomes[38].

Point estimates were reported as the mean across all iterations. The 95% credible intervals (CrIs) for costs, QALYs, and ICERs were derived from the simulated outcome distributions using the equal-tailed 2.5th and 97.5th percentiles. Decision uncertainty was summarised using cost-effectiveness scatter plots and cost-effectiveness acceptability curves (CEACs), illustrating the probability that CYP2C19-guided DAPT is cost-effective across alternative willingness-to-pay thresholds[20].

Decision analytic model validation

We assessed face validity [39] of the decision-analytic model structure by presenting the decision problem and conceptual model to the expert group (clinical and people with ACS). Face validity was based on consensus agreement from four experts actively involved in pharmacogenomics and clinical practice.

To confirm the decision-analytic model was coded accurately, the decision-analytic model was independently built using two pieces of software (and two analysts): R(JH) and Excel (AM). The model outputs were then compared to identify and resolve any discrepancies. Technical validity was assessed by an independent decision analyst external to the research team (personal communication: Stuart J Wright), using the TECH-VER checklist (see Supplementary Appendix 3) [40]. The model was deemed technically valid when no outstanding issues remained that affected the returned expected costs and QALYs for the intervention and comparator in the main analysis. The R programming language implementation of our decision-analytic model is available at: <https://github.com/JBHilton/pg-ap-analytics>.

Results

Base-case analysis

For the STEMI population (n = 41,690), CYP2C19-guided DAPT generated health gains of 0.0439 additional QALYs per patient, at slightly higher lifetime costs £25 compared with current strategy representing an ICER of £569 per QALY gained (see Table 2). For the UA/NSTEMI population (n = 61,248), CYP2C19-guided DAPT strategy generated health gains of 0.0358 additional QALYs, at lifetime costs £83 compared with the current strategy, generating an ICER of £2,318 per QALY gained (Table 2). In the model, the CYP2C19-guided approach produced modest absolute differences in first-year outcomes relative to current practice. Estimated reductions were approximately two reinfarctions and seven deaths per 1000 STEMI patients and around three reinfarction and six deaths per 1000 UA/NSTEMI patients following PCI. Bleeding outcomes improved in both cohorts, with 1.5 fewer major bleed and 13 fewer minor bleeds per 1000 STEMI cases and one fewer major and minor bleed per 1000 UA/NSTEMI cases (Table 3).

Table 2
Base-case deterministic results for STEMI and UA/NSTEMI

DAPT strategy	Costs (£; per patient)	QALYs (per patient)	Incremental costs (£; per patient)	Incremental QALYs (per patient)	ICER (£ per QALY)	Costs (£; per patient)	QALYs (per patient)	Incremental costs (£; per patient)	Incremental QALYs (per patient)	ICER (£ per QALY)
	Discounted					Undiscounted				
STEMI										
current DAPT	£24,780	6.301	£25	0.0439	£569	£31,528	8.073	£69	0.0571	£1,208
CYP2C19-guided DAPT	£24,805	6.345				£31,597	8.130			
UA/NSTEMI										
current DAPT	£21,443	6.262	£83	0.0358	£2,318	£26,692	7.942	£114	0.0464	£2,456
CYP2C19-guided DAPT	£21,526	6.297				£26,806	7.989			

Table 3
Number of clinical events each year for 1,000 patients for each DAPT strategy in STEMI and UA/NSTEMI patients

DAPT strategy	Reinfarction (95% credible interval)	Stroke (95% credible interval)	Major bleed (95% credible interval)	Minor bleed (95% credible interval)	Deaths (95% credible interval)
STEMI					
Current DAPT	55.8(45.2–67.6)	13.1 (10.4, 16.1)	24.6 (15.5, 35.6)	85.6 (63.4, 107.3)	85.9 (78.2, 94.2)
CYP2C19-guided DAPT	54.2 (41.6–69.4)	12.7 (10.1, 15.7)	23.2 (14.6, 33.9)	72.4 (54.6, 92.3)	79.4 (66.0, 95.4)
UA/NSTEMI					
Current DAPT	38.4 (31.2, 46.5)	6.7 (5.9, 7.5)	24.53 (15.76, 35.12)	18.14 (10.25, 28.03)	48.7 (45.3, 52.5)
CYP2C19-guided DAPT	35.3 (26.8, 45.5)	6.5 (5.6, 7.6)	24.28 (15.51, 35.06)	17.07 (9.65, 26.83)	43 (35.7, 52.7)
^a Credible interval for events, shown in brackets, were derived from the distribution of simulation outputs. Abbreviations: STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; NSTEMI, Non-ST elevation myocardial infarction; DAPT, dual antiplatelet therapy.					

<< Table 2

<< Table 3

Sensitivity analysis

In both STEMI and UA/NSTEMI cohorts, CYP2C19-guided DAPT remained cost-effective, when viewed against a threshold of £20,000 per QALY gained, across all one-way sensitivity analyses. In the STEMI subgroup, the NMB was most influenced by the risk of ischaemic events and health-state utilities; varying these inputs produced the largest (though still modest) changes in NMB. A very similar pattern was observed for UA/NSTEMI, where NMB was driven primarily by reinfarction probabilities (Markov/early decision-tree components), major bleeding risk parameters, and utilities for long-term health states (see Supplementary Appendix 4).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis indicated that the cost-effectiveness results were robust to parameter uncertainty. Supplementary Appendix 5 shows the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) from probabilistic analysis of base case scenario. At a willingness-to-pay threshold of £20,000 per QALY, CYP2C19-guided DAPT was the cost-effective strategy in 87.6% and 94.3% of simulations in the STEMI and UA/NSTEMI populations, respectively.

For the STEMI population (n = 41,690), CYP2C19-guided DAPT generated health gains (0.0428 additional QALYs per person; 95% Credible Interval – 0.0357 to 0.1095), increasing mean QALYs from 6.30 (95% Credible Interval 6.14 to 6.44) with current prescribing to 6.34 (95% Credible Interval 6.16 to 6.50) with testing, at a small increase in discounted lifetime costs of £32 per person (95% Credible Interval –£260 to £284). This resulted in an ICER of £2,507 per QALY gained (95% Credible Interval –£19,313 to £21,047) and a positive NMB at a £20,000 per QALY threshold (Table 4). Findings were consistent in the UA/NSTEMI population (n = 61,248), with similarly modest QALY gains (incremental 0.0354; 95% Credible Interval – 0.0088 to 0.0718), small additional costs (£95 per person), and an ICER £2749 (95% Credible Interval –£4215 to £10711) per QALY, suggesting CYP2C19-guided DAPT is cost-effective in both populations.

Table 4

Probabilistic sensitivity analysis results for CYP2C19-guided treatment versus current DAPT in STEMI and UA/NSTEMI (per person)

DAPT strategy	Mean discounted cost (95% credible interval)	Mean discounted QALYs (95% credible interval)	Incremental cost, £ (95% credible interval)	Incremental QALYs (95% credible interval)	ICER (95% credible interval)	Net Monetary Benefit £, (95% credible interval)	Incremental Net Monetary Benefit (95% credible interval)
STEMI							
Current DAPT	£24768 (£23074 - £26644)	6.30(6.14, 6.44)	32(-260, 284)	0.0428 (-0.0357, 0.1095)	2507 (-19313, 21047)	£101,245 (£97,427–£104,718)	£823 (-£506–£1,979)
CYP2C19-guided DAPT	£24801 (£23079 - £26706)	6.34(6.16, 6.50)				£102,069 (£98,009–£105,820)	
UA/NSTEMI							
Current DAPT	21443 (19956, 23140)	6.26 (6.13, 6.37)	82(-59, 241)	0.0354 (-0.01, 0.07)	2749 (-4215, 10711)	£103,790 (£100,641–£106,617)	£614 (-£157–£1,270)
CYP2C19-guided DAPT	21526 (20039, 23247)	6.30 (6.16, 6.42)				£104,404 (£101,149–£107,365)	

In terms of monetary outcomes, CYP2C19-guided DAPT also produced higher net monetary benefit (NMB) than current prescribing in both cohorts (Table 4). In the STEMI population, mean NMB at a £20,000 per QALY threshold was £101,245 per person with current DAPT and £102,069 per person with CYP2C19-guided DAPT, corresponding to an incremental NMB of £823 per person (Table 4). When scaled to the full STEMI cohort (n = 41690), this equated to a total NMB of £4.22 billion for current DAPT and £4.26 billion for CYP2C19-guided DAPT. In the UA/NSTEMI population, mean NMB was £103,790 per person (95% CrI £100,641 to £106,617) with current DAPT and £104,404 per person (95% CrI £101,149 to £107,365) with CYP2C19-guided DAPT, yielding an incremental NMB of £614 per person (95% CrI –£157 to £1,270). Scaled to the UA/NSTEMI cohort (n = 61,248), total NMB was £6.36 billion under current DAPT and £6.39 billion with CYP2C19-guided DAPT, corresponding to a total incremental NMB of £37.6 million (Table 4). The results for the PSA using undiscounted costs and QALYs are presented in the Supplementary Appendix 6.

<< Table 4

Scenario analysis

Across the probabilistic scenario analyses, the conclusion that CYP2C19-guided DAPT is cost-effective in the STEMI population remained unchanged, with the probability of cost-effectiveness at a £20,000 per QALY threshold consistently high. In the scenario analysis when the alternative DAPT proportion was varied, CYP2C19-guided DAPT remained cost-effective, with an ICER of £9,924 per QALY and a probability of cost-effectiveness of 87.4%. When the prevalence of CYP2C19 loss-of-function alleles was increased to 56.8% in STEMI group, the strategy remained cost-effective (ICER £2,269 per QALY; and a probability of cost-effectiveness of 91%). When the cost of the point-of-care test was doubled to £250, and under the ticagrelor off-patent price assumption, CYP2C19-guided DAPT continued to be favoured, with probabilities of cost-effectiveness remaining high in both scenarios. Probabilistic scenario analysis results for the UA/NSTEMI population show a consistent pattern across all scenarios with the CYP2C19-guided DAPT remaining cost-effective.

In the scenario assuming price parity between ticagrelor and clopidogrel, the PSA produced results that differed in magnitude but were consistent with the base-case conclusions. In the STEMI population, the incremental cost was £202 and the incremental QALY gain was 0.043, giving an ICER of £2,036 per QALY. Similar findings were observed for the UA/NSTEMI population, with an ICER of £5,675 per QALY. The probability of cost-effectiveness was 85.5% in STEMI and 92.4% in UA/NSTEMI (see Supplementary Appendix 7).

Discussion

This study has suggested that CYP2C19-guided DAPT in PCI-ACS is highly likely to be a good use of the NHS budget when judged against commonly used thresholds for cost-effectiveness (£20,000 per QALY) in England also showing positive NMB. In both STEMI and UA/NSTEMI populations, the strategy yielded modest but measurable gains in QALYs at a modest additional cost. Results were more influenced by the assumed value of inputs representing treatment effectiveness than costs. Our findings also indicated that the economic value of CYP2C19-

guided DAPT was sensitive to population genetic composition but remained cost-effective. This finding does underline the importance of considering subgroup variability in multi-ethnic health systems.

Our decision-analytic model followed the structure of NICE guideline NG185[2], using the same evidence base for risk estimates where this provided the most reliable data. Estimates of life expectancy and total costs for individuals receiving current DAPT were consistent the results reported in NG185 which supports the external validity of the analysis.

Previous economic evaluations of CYP2C19-guided DAPT have often assumed universal prescribing patterns. Kazi et al[18]. modelled scenarios in which all participants received clopidogrel, prasugrel, or ticagrelor, finding that CYP2C19-guided escalation from clopidogrel yielded modest health gains of between 0.03 to 0.06 QALYs, with ICERs of US\$30,200 to US\$52,600 per QALY gained, appearing less favourable than universal ticagrelor. Similarly, Kim et al[41]. compared universal clopidogrel, universal ticagrelor, and CYP2C19-guided therapy, reporting gains of 0.012 to 0.016 QALYs and ICERs of Singaporean \$72,000 to Singaporean\$82,000 per QALY gained relative to clopidogrel. In contrast, de-escalation strategies have demonstrated more favourable outcomes. Limdi et al[17]. showed that switching non-carriers from ticagrelor to clopidogrel generated 0.011 QALYs and substantial drug cost savings, with an ICER of US\$42,365 per QALY gained, whereas universal ticagrelor was inefficient, with a ratio exceeding US\$227,000 per QALY gained. Studies by AlMukdad et al[42]. and Dong et al[16]. found de-escalation to be either dominant or associated with ICERs as low as US\$1,383 per QALY gained, with cost savings in more than 60% of simulations in the PSA. Building on this evidence, our analysis was structured around current NHS prescribing patterns in two ACS subgroups[1]. In STEMI, more than 78% of individuals received prasugrel or ticagrelor, making de-escalation the predominant mechanism through which testing influences cost-effectiveness. In UA/NSTEMI, approximately half of the participants were prescribed clopidogrel and half prasugrel or ticagrelor, resulting in a meaningful proportion of escalation. By capturing both escalation and de-escalation within realistic treatment distributions, the model provides a closer representation of routine clinical practice and supports the cost-effectiveness of CYP2C19-guided testing in both subgroups, underlining its potential to enhance personalised prescribing within the NHS.

Accounting for uptake of genetic testing to inform prescribing can influence cost-effectiveness results, as lower adoption, whether due to patient or clinician preferences or system-level constraints, can increase the mean cost per person. Most published evaluations of CYP2C19-guided DAPT assumed universal complete uptake and perfect implementation of test results, without accounting for delays, laboratory capacity, or partial adoption[17, 41, 43, 44]. In contrast, our analysis accounted for imperfect uptake, applying a 93% rate for both ordering and acting on test results, based on evidence that complete adherence is unlikely in routine care[29]. Perfect uptake was examined in sensitivity analyses. The evaluation was based on a point-of-care CYP2C19 test with results available in approximately 80 minutes, which clinicians judged to have a clinically negligible turnaround time. Test accuracy was assumed to be 100%, consistent with UK validation of the GeneDrive platform showing complete concordance with reference laboratory testing and a failure rate below 1%[22]. Dong et al.[16] took a similar approach, explicitly modelling clinical practice implementation scenarios. They found that adherence to escalation had little impact on cost-effectiveness, whereas de-escalation was the primary driver of value, highlighting the importance of ensuring reliable adoption of de-escalation in practice.

In the base case, we valued antiplatelet medicines using 2025 prices, but generic entry particularly for ticagrelor and prasugrel has the potential to reduce unit costs relative to those assumed. To test whether our conclusions were driven by contemporaneous list prices, we explored alternative pricing in scenario analyses, including an off-patent price assumption. Under these assumptions, CYP2C19-guided DAPT remained cost-effective, with only small changes in incremental costs and QALYs and ICERs remaining well below the £20,000 per QALY threshold. This suggests that the main conclusions are robust to plausible reductions in P2Y₁₂-inhibitor prices, although future updates should reflect observed NHS purchase prices as these continue to evolve.

To implement pharmacogenetic testing at scale, health care systems require robust infrastructure to integrate results into clinical practice, as well as secure storage of genetic information for future use[45]. As no costing studies have fully captured the actual cost associated with point-of-care genotype testing in routine settings, uncertainty remains regarding potential overheads. To account for this, we conducted a sensitivity analysis that doubled the unit cost of testing. Our findings indicated that genotype-guided DAPT remains cost-effective, even when we increased the assumed cost of the test. Other studies that included point-of-care testing in sensitivity analyses similarly found that while test cost was an influential parameter, genotype-guided therapy remained cost-saving across plausible ranges, with no change in the overall conclusion[14–16, 44]. In contrast, Kazi et al.[18] reported that substantially higher test prices could alter the preferred strategy, suggesting greater cost sensitivity in settings with higher testing costs. Collectively, these findings support the robustness of CYP2C19-guided DAPT and indicate that, within the NHS context, its cost-effectiveness is unlikely to be undermined by variations in test pricing.

Strengths and limitations

This is the first UK-based economic evaluation to estimate the value of CYP2C19-guided DAPT using NHS-specific costs and aligned directly with NICE guideline NG185[2] for acute coronary syndromes (ACS). By embedding CYP2C19-guided DAPT within current national pathways

and commissioning structures, the analysis provides a policy-relevant assessment grounded in clinical practice in the NHS in England. The decision-analytic model was co-designed and face-validated with key stakeholders, employed a best-practice hybrid structure to capture both early post-PCI events and long-term recurrence, and stratified outcomes by ACS subtype to reflect differing baseline risks. Importantly, the model incorporated several implementation parameters, such as variation in genotype prevalence by ethnicity, test-ordering workflows, and imperfect adherence, addressing limitations of earlier models that assumed universal uptake. Transparency and reproducibility were ensured through internal and cross-validation, and all code is publicly available in R to facilitate external scrutiny. The work also aligns with the NHS Genomic Medicine Service strategy and contributes to the broader precision medicine agenda in cardiovascular care.

Several limitations should be acknowledged. The decision-analytic model relied on publicly available data sources, which vary in robustness and generalisability. The decision-analytic model applied differential effectiveness of dual antiplatelet therapy only during the 12-month treatment period, due to lack of robust data on long-term benefit, potentially underestimating downstream effects. Baseline event risks were drawn from historical UK audit data and secondary sources that were not always specific to clopidogrel users; in some cases, assumptions were required to estimate short- and long-term risks. While sensitivity analyses explored alternative inputs, these approximations may not fully reflect current clinical practice.

Prescribing patterns for DAPT were based on BCIS audit data from PCI centres, with the most recent data from 2022, which may not capture regional or temporal variation across England. In addition, estimates of CYP2C19 genetic testing uptake were informed by a discrete choice experiment among general practitioners and pharmacists, reflecting stated preferences rather than observed behaviours; actual uptake in practice may differ.

Conclusion

CYP2C19-guided DAPT was consistently more effective and cost-effective than current prescribing practice for both STEMI and UA/NSTEMI populations, with ICERs well below a defined willingness-to-pay threshold of £20,000 per QALY gained. Results were robust to variation in antiplatelet prescribing patterns, test uptake, unit costs, and allele frequencies, supporting their external validity. Scenario analyses incorporating higher frequencies of *CYP2C19* loss-of-function alleles, as seen in Asian populations led to increased ICERs but retained cost-effectiveness. These findings should, however, not assumed to be directly generalisable to all jurisdictions or patient populations.

Abbreviations

ABCB1	
ATP-binding cassette subfamily B member 1	
ACS	
Acute coronary syndrome	
ACS-PCI	
Acute coronary syndrome treated with percutaneous coronary intervention	
BNF	
British National Formulary	
BRC	
Biomedical Research Centre	
BCIS	
British Cardiovascular Intervention Society	
CEAC	
Cost-effectiveness acceptability curve	
CHEERS	
Consolidated Health Economic Evaluation Reporting Standards	
CI	
Confidence interval	
CYP2C19	
Cytochrome P450 2C19	
DAPT	
Dual antiplatelet therapy	
DISPERSE-2	
Dose confirmation Study Assessing Anti-Platelet Effects of AZD6140 versus Clopidogrel in Non–ST-segment Elevation Myocardial Infarction	

HR
Hazard ratio
ICER
Incremental cost-effectiveness ratio
ISPOR-SMDM
International Society for Pharmacoeconomics and Outcomes Research & Society for Medical Decision Making
LoF
Loss-of-function (allele)
NG185
NICE guideline 185 (Acute coronary syndromes)
NHS
National Health Service
NICE
National Institute for Health and Care Excellence
NIHR
National Institute for Health and Care Research
NMB
Net monetary benefit
NSTEMI
Non-ST-segment elevation myocardial infarction
OR
Odds ratio
P2Y₁₂
P2Y₁₂ receptor
PCI
Percutaneous coronary intervention
PLATO
Platelet Inhibition and Patient Outcomes
PSA
Probabilistic sensitivity analysis
PSSRU
Personal Social Services Research Unit
QALY
Quality-adjusted life-year
SE
Standard error
STEMI
ST-segment elevation myocardial infarction
TECH-VER
Technical verification checklist
UA
Unstable angina
UK
United Kingdom
US
United States

Declarations

Ethics approval and consent to participate

This study did not involve the collection of primary clinical data from patients, human tissue, or animals.

Consent for publication

Not applicable.

Availability of data and materials

This study did not collect primary data. The model code used for the analysis is available at: <https://github.com/JBHilton/pg-ap-analytics>.

Competing interests

RB reports consultancy fees (to employer) from Siemens Healthineers, Roche Diagnostics, Abbott Point of Care, LumiraDx, Aptamer Group, Prolight Diagnostics, bioMérieux, and Radiometer. RB has received research grants (to employer) from Siemens Healthineers, Roche Diagnostics, and Abbott Point of Care, and has participated in educational activities (fees to employer) with Roche Diagnostics and Abbott Point of Care. All other authors declare no competing interests.

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Author's Contributions

All the authors contributed to the conceptualisation and validation of the economic model. RB, JM and WGN provided clinical expertise, advising on ACS care pathways and treatment practice. AM, MR and JH, conducted formal analysis. KP, JM and WGN secured funding. AM, MR and KP designed study methodology which was supervised by KP. AM and JH undertook the analysis in Excel and R. AM led writing original draft and all the authors contributed to reviewing and editing the manuscript and approved the final version. KP acts as the guarantor for this work.

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Figures

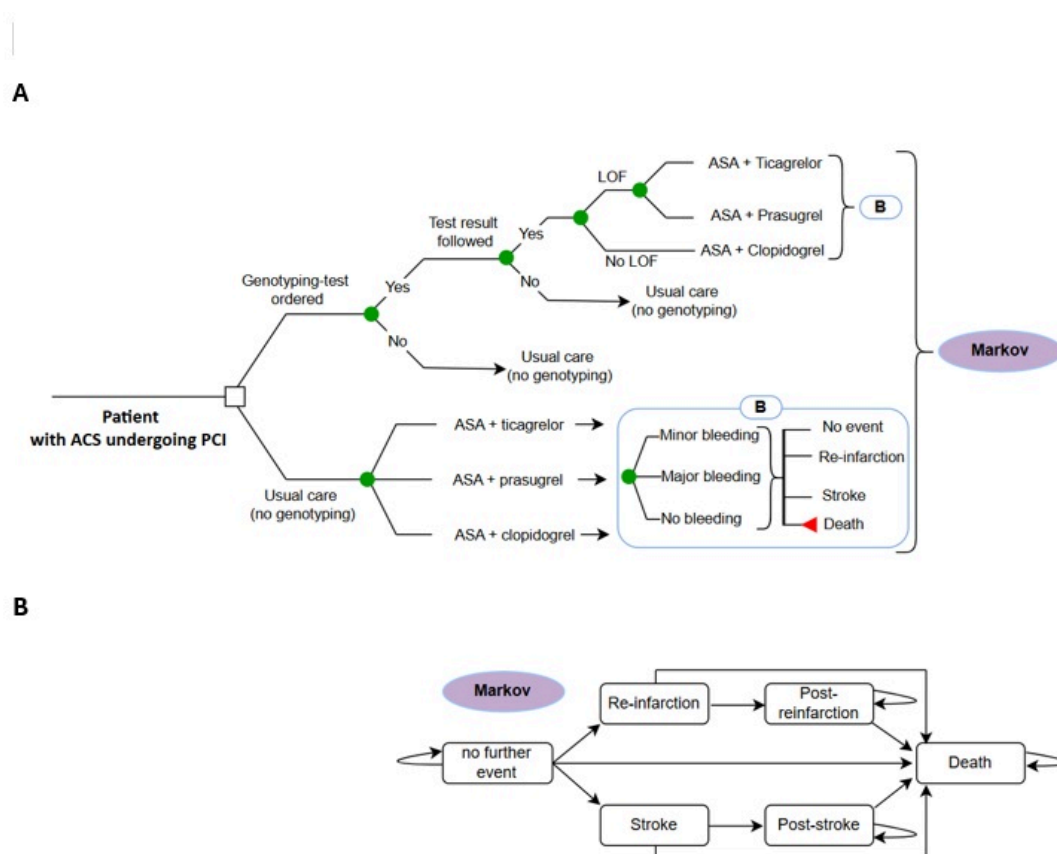


Figure 1. Decision-analytic model structure, **A**, 1-year decision tree; **B**, lifetime Markov model; Patients who survive at 12 months transition into the Markov model, entering the health state corresponding to their terminal event in the decision tree. Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; ASA, acetylsalicylic acid; LoF, loss of function allele in CYP2C19.

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Supplementary Files

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